

Workshop HCV

Ferrara 26-29 maggio 2017

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Razionale

- Il paziente con epatite HCV correlata presenta un quadro clinico complesso : numerosi dati epidemiologici correlano infatti l'infezione da HCV a problematiche extraepatiche quali glomerulonefrite, artropatie , crioglobulinemie, malattie cardiovascolari e neurologiche
- A causa della complessità di questi pazienti diventa essenziale definire un approccio multidisciplinare, coinvolgendo in questo percorso anche altri specialisti
- Per tale motivo abbiamo deciso di effettuare due workshop di confronto fra gastroenterologi ed infettivologi e medici di due branche specialistiche, nefrologia e reumatologia
- Scopo di questi incontri è fornire agli specialisti non epatologi nozioni sulle nuove terapie antivirali dirette, efficaci e sicure, ma anche sensibilizzare a ricercare l'HCV nei loro pazienti ed eventualmente trattare quelle situazioni cliniche di loro competenza, che potrebbero essere correlate ,anche indirettamente, alla infezione HCV e che potrebbero giovare di una terapia antivirale.
- Si cercherà di costruire un percorso condiviso per proporre la terapia anche a questi pazienti , afferenti ad altri specialisti non epatologi .

Hepatic

Extrahepatic

HCV

Inflammation

Steatosis

Fibrosis/Cirrhosis

Hepatocellular Carcinoma

Cholangiocellular Carcinoma

Mixed cryoglobulinemia

Membrano-proliferative
Glomerulonephritis

B cell Lymphoma

Sicca Syndrome

Autoimmune Thyroiditis

Atherosclerosis

Insulin resistance /
Type 2 diabetes

Myocardial Dysfunction

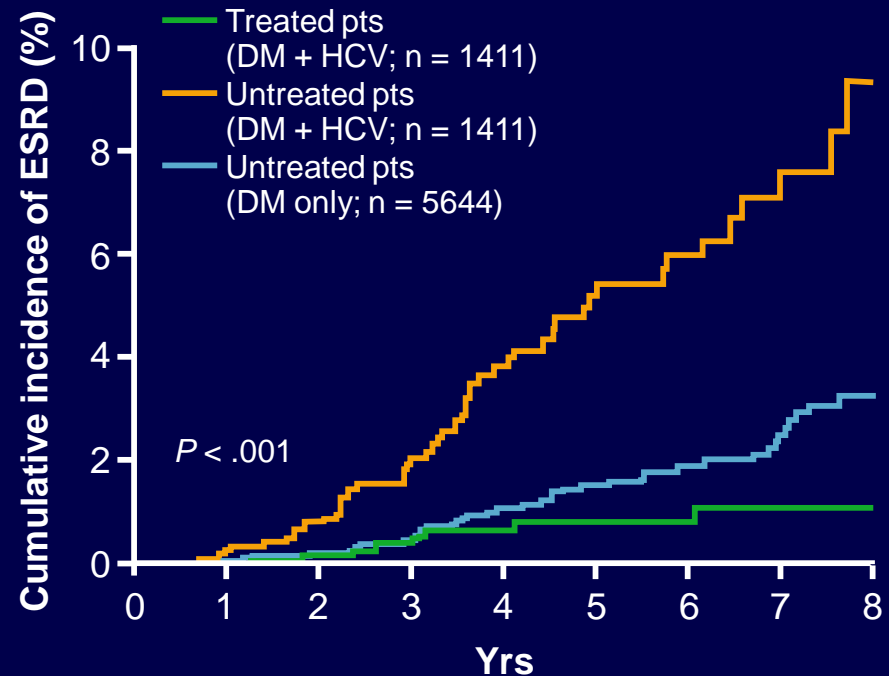
Cognitive impairment

Fibromyalgia Syndrome

Benefits of HCV Therapy Extend Beyond the Liver: Diabetes

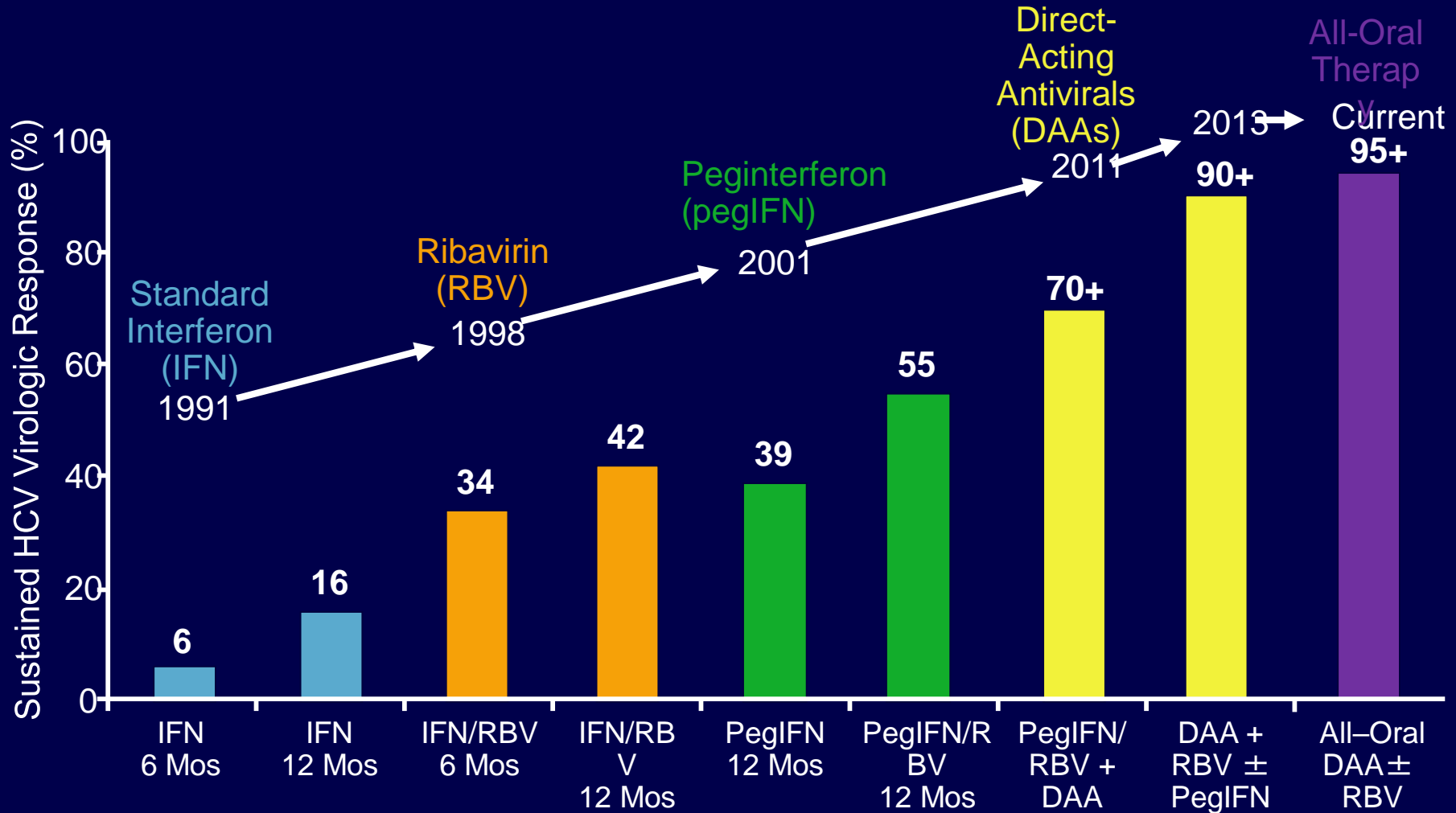
- HCV cure significantly reduces incidence of type 2 DM^[1]
 - HCV pts have 2-3 x greater odds of DM^[2]
- SVR may prevent and improve IR^[3]
 - IR and DM increase risk and rate of fibrosis^[2]
- PegIFN + RBV associated with improved renal/cardiovascular outcomes in pts with DM + HCV^[4]

ESRD in DM Pts Treated or Untreated With PegIFN + RBV^[4]



1. Arase Y, et al. Hepatology. 2009;49:739-744.
2. Brandman D, et al. Diabetes Care. 2012;35:1090-1094.
3. Aghemo A, et al. Hepatology. 2012;56:1691-1687.
4. Hsu YC, et al. Hepatology. 2014;59:1293-1302.

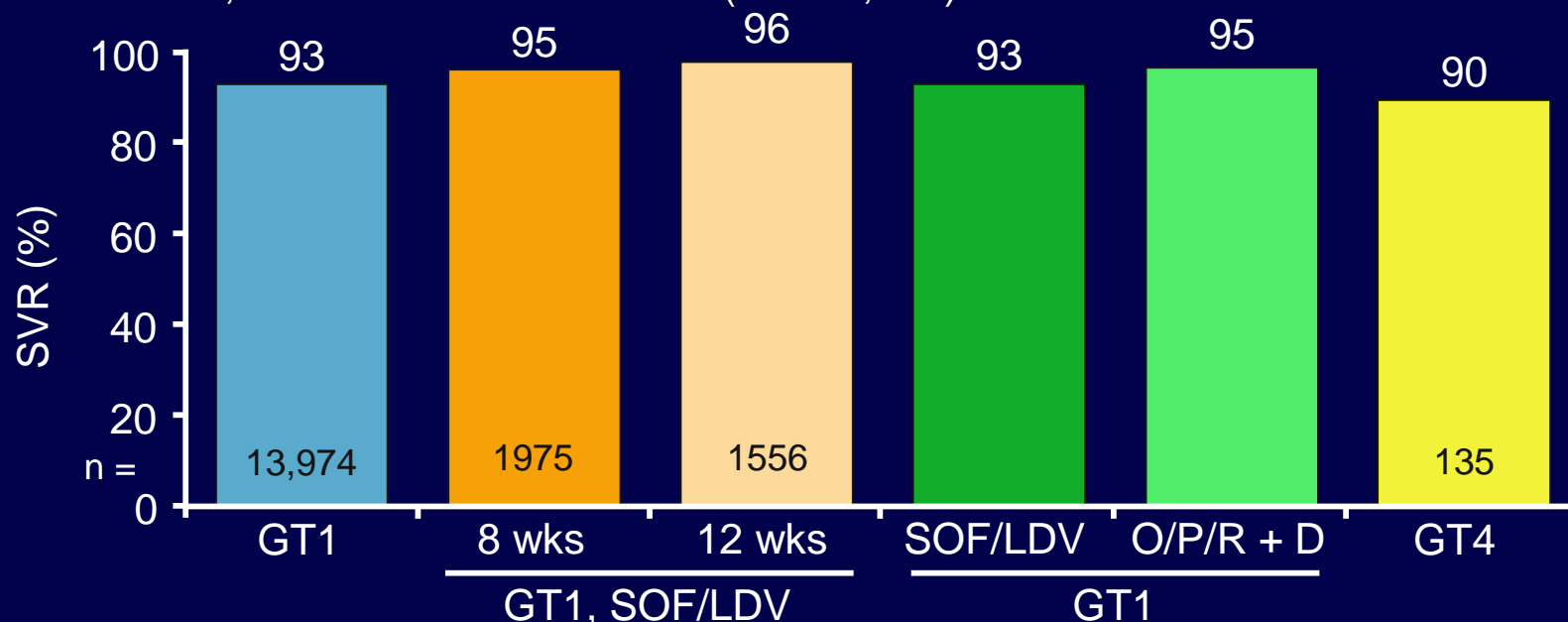
Current All-Oral Therapies Highly Effective, Simple, Well Tolerated



References in slidenotes

Real-World HCV Treatment in the US VA Healthcare System

- Analysis of real-world SVR for pts with GT1-4 HCV treated with SOF + RBV ± pegIFN, SOF/LDV, or OBV/PTV/RTV + DSV (N = 17,487)^[1]



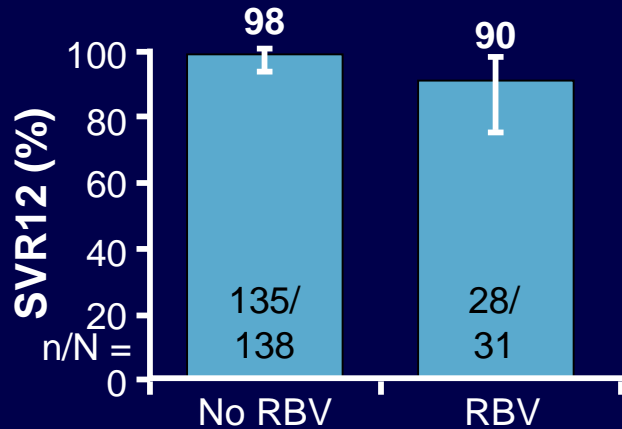
- Analysis of HCV treatment in VA healthcare system (N = 107,079)^[2]
 - Dramatic increases in HCV treatment in 2014-2015 vs 1999-2013 (1999-2011, 1989 to 7196 treatments/yr; 2014, 9180 treatments; 2015, 31,028 treatments)
 - Related to improved antiviral efficacy and availability of funding

1. Ioannou GN, et al. AASLD 2016. Abstract 21. Reproduced with permission.

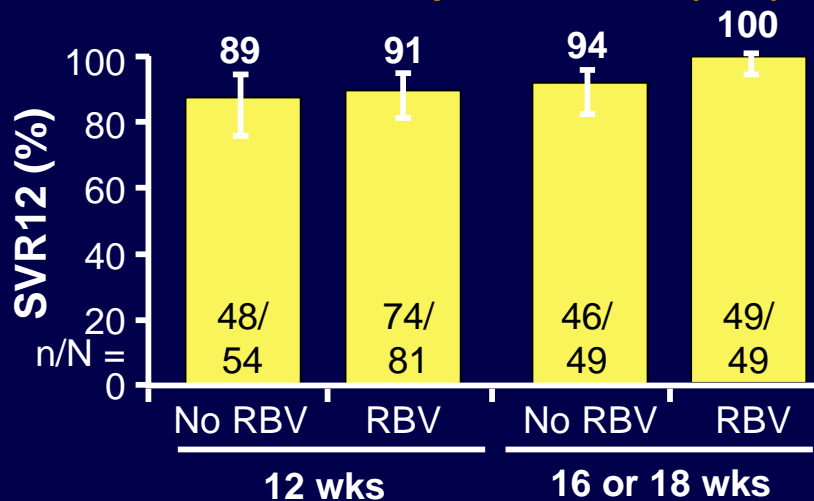
2. Moon AM, et al. AASLD 2016. Abstract 227.

Elbasvir/Grazoprevir in Compensated Cirrhosis: SVR12

Treatment Naive Pts; 12 Wks (FAS)



Treatment Experienced Pts (FAS)

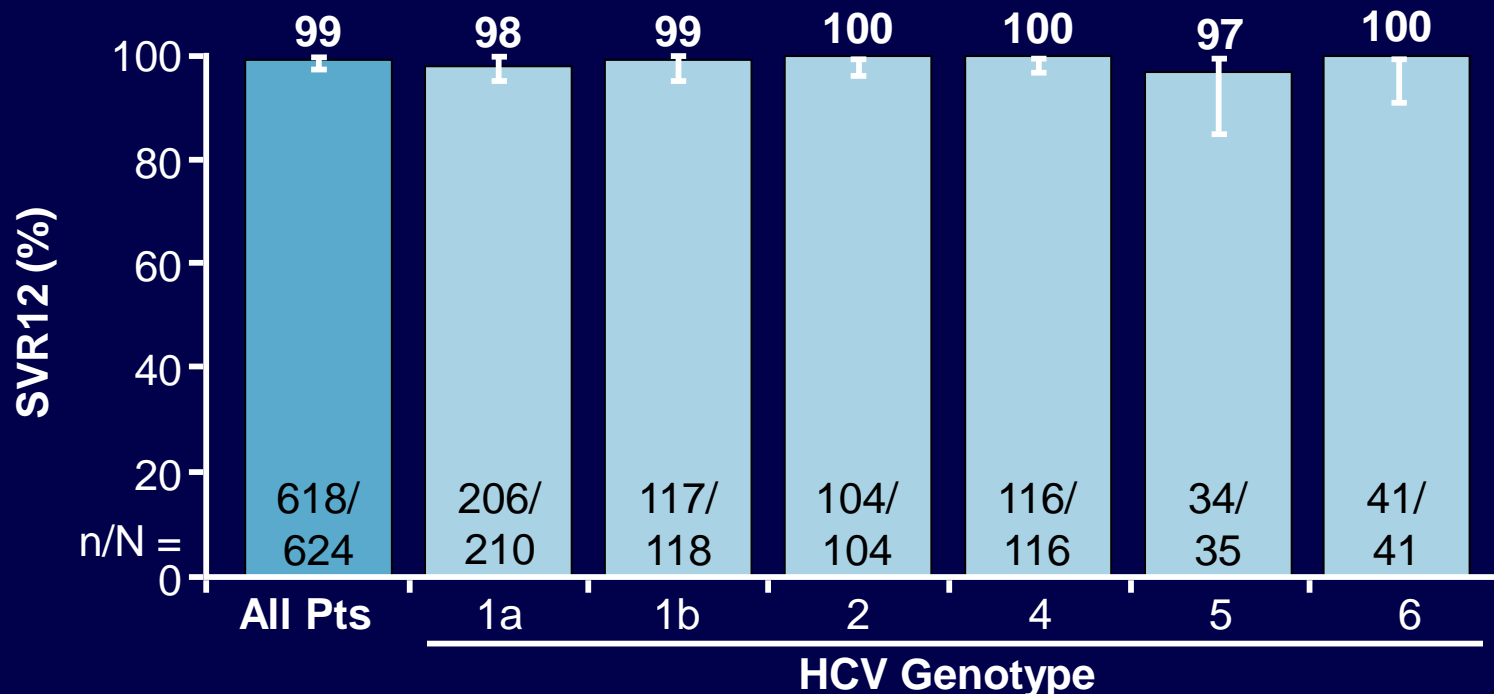


- Treatment-naive pts:** SVR12 rates similar regardless of RBV use, HCV subtype in FAS and regardless of platelets, cirrhosis determination method, *FibroScan* score in mFAS
 - SVR12 rate range across subgroups treated without RBV: 96% to 100%
- Previous relapsers (mFAS):** SVR12 rates not affected by treatment duration or RBV use
- Previous nonresponders (mFAS):** SVR12 rates lower with 12-wk, no RBV vs 16/18-wk, + RBV treatment
 - GT1: 92% vs 100%
 - GT4: 67% vs 100%



ASTRAL-1: SVR12 With Sofosbuvir/ Velpatasvir in GT1, 2, 4, 5, 6 HCV

- Double-blind, placebo-controlled trial
 - All pts with GT5 HCV allocated to active Tx because few pts in this group (n = 35)
 - Key baseline characteristics: cirrhosis 19%; Tx exp'd 32%; BL NS5A RAVs 42%
- No impact of cirrhosis, Tx experience, BL NS5A RAVs on SVR rates



EASL Guidelines 2016

Highlights Summary

All patients
must be considered for
treatment of Hepatitis C

**First all oral IFN-free
HCV treatment
recommendations**
SOF based regimens
recommended across
genotypes, disease
stages and patient
populations

**Acute treatment
recommendation**
8 wks SOF+NS5A
(LDV/SOF, SOF/VEL and
SOF+DCV), 12 wks
SOF+NS5A in co-
infected and/or patients
with VL above 1M

**Sofosbuvir as
retreatment backbone**
due to high barrier to
resistance

**Guidance on treatment
of patients with
advanced disease**
MELD classification cut
off 18-20

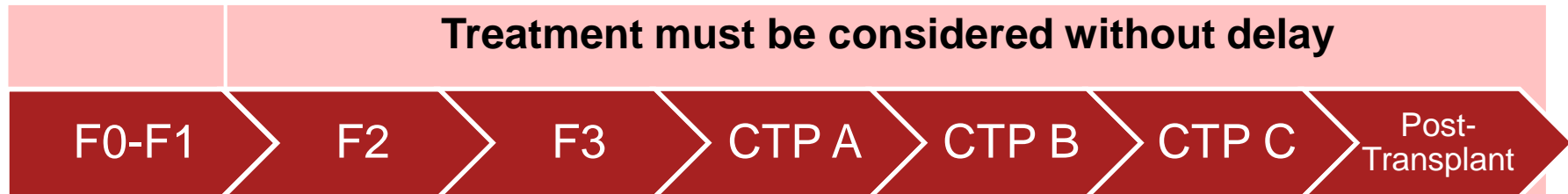
Screening strategies for
HCV infection should be
defined according to
the local epidemiology
of HCV infection, ideally
within the framework of
national plans

HCV core antigen
is a surrogate marker of
HCV replication and can
be used instead of HCV
RNA to diagnose acute
or chronic infection
when HCV RNA assays
are not available or not
affordable

Elimination:
To achieve HCV
elimination will require
national plans together
with unrestricted access
to treatment

Indications for treatment of chronic hepatitis C in 2016: Who should be treated and when?

- **ALL** patients must be considered for treatment of Hepatitis C
- To achieve HCV elimination will require national plans together with forecasted budgeting to expedite unrestricted access to treatment



Additional population that should be prioritised:

- HIV Coinfection
- HBV Coinfection
- Clinically significant extra-hepatic manifestations
- High transmitters:
 - Active injection drug users
 - MSMs
 - Prisoners
 - Women of child-bearing age
 - Haemodialysis patients
 - Incarcerated individuals



Approved HCV drugs in the Europe 2016

First all-oral, IFN-free treatment recommendations

Product	Presentation	Posology
Sofosbuvir	Tablet containing 400 mg of sofosbuvir	One tablet once daily (morning)
Ledipasvir/sofosbuvir	Tablet containing 400 mg of sofosbuvir and 90 mg of ledipasvir	One tablet once daily (morning)
Sofosbuvir/velpatasvir	Tablet containing 400 mg of sofosbuvir and 100 mg of velpatasvir	One tablet once daily (morning)
Paritaprevir/ombitasvir/ritonavir	Tablets containing 75 mg of paritaprevir, 12.5 mg of ombitasvir and 50 mg of ritonavir	Two tablets once daily (morning)
Dasabuvir	Tablets containing 250 mg of dasabuvir	One tablet twice daily (morning and evening)
Grazoprevir/elbasvir	Tablets containing 100 mg of grazoprevir and 50 mg of elbasvir	One tablet twice daily (morning and evening)
Daclatasvir	Tablets containing 30 or 60 mg of daclatasvir	One tablet once daily (morning)
Simeprevir	Capsules containing 150 mg of simeprevir	One capsule once daily (morning)
Ribavirin	Capsules containing 200 mg of ribavirin	Two capsules in the morning and 3 in the evening if body weight <75 kg Or Three capsules in the morning and 3 in the evening if body weight ≥75 kg

PEGASYS (PegIFN- α 2a) Roche Products Limited, SmPC, November 2014; VIRAFERON-PEG (PegIFN- α 2b), Merck Sharp & Dohme Limited. SmPC June 2014; COPEGUS (ribavirin) Roche Products Limited. SmPC, February 2015; REBETOL (ribavirin) Merck Sharp & Dohme Limited. SmPC May 2014; OLYSIO (simeprevir), Janssen Products LP. SmPC, March 2015; Limited. DAKLINZA (daclatasvir), Bristol-Myers Squibb Pharmaceutical. SmPC October 2014) HARVONI (ledipasvir/sofosbuvir), Gilead Sciences Europe Ltd. SmPC, November 2014 VIEKIRAX (ombitasvir/paritaprevir/ritonavir), AbbVie Ltd. SmPC, January 2015 EXVIERA (dasabuvir), AbbVie Ltd. SmPC, January 2015); SOVALDI (sofosbuvir), Gilead Sciences Europe Ltd. SmPC, March 2015; HARVONII (ledipasvir/sofosbuvir), Gilead Sciences Europe Ltd. SmPC, November 2015; EASL Recommendations on Treatment of Hepatitis C 2015; Journal of Hepatology 2015 vol. 63, 199–236



Drug-Drug Interactions

www.hep-druginteractions.org



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DRUG INTERACTION CHARTS

A sample drug interaction chart with columns for drug names and rows for interaction types. The chart is tilted and shows a grid of text and symbols.

Access our comprehensive, user-friendly,
free, drug interaction charts

[CLICK HERE](#)

Providing clinically useful, reliable,
up-to-date, evidence-based information



Drug-Drug interactions: Lipid lowering drugs

	SOF	LDV/ SOF	SOF/ VEL	OBV/PT V/RTV+ DSV	GZR/ EBR	DCV	SMV
Atorvastatin	◆	■	■	●	■	■	■
Bezafibrate	◆	◆	◆	◆	◆	◆	◆
Ezetimibe	◆	◆	◆	■	◆	◆	◆
Fenofibrate	◆	■	■	◆	■	◆	◆
Fluvastatin	◆	■	■	■	■	■	◆
Gemfibrozil	◆	◆	◆	●	■	◆	◆
Lovastatin	◆	■	■	●	■	■	■
Pitavastatin	◆	■	■	■	◆	■	■
Pravastatin	◆	■	◆	■	◆	■	■
Rosuvastatin	◆	●	■	■	■	■	■
Simvastatin	◆	■	■	●	■	■	■

SOF: sofosbuvir; LDV: ledipasvir; VEL: velpatasvir; OBV: ombitasvir; PTV: paritaprevir; DSV: dasabuvir; GZR: grazoprevir; EBR: elbasvir; DCV: daclatasvir; SMV: simeprevir




- ◆ No clinically significant interaction expected
- Potential interaction which may require a dosage adjustment, altered timing of administration or additional monitoring
- These drugs should not be co-administered.



Drug-Drug interactions: HCV DAAs and cardiovascular drugs

		SOF	LDV/ SOF	SOF/ VEL	OBV/PT V/RTV+ DSV	GZR/ EBR	DCV	SMV
Antiarrhythmics	Amiodarone	●	●	●	●	■	●	■
	Digoxin	◆	■	■	■	◆	■	■
	Flecainide	◆	◆	◆	■	◆	◆	■
	Vernakalant	◆	◆	◆	■	◆	◆	◆
Antiplatelet and anticoagulants	Clopidogrel	◆	◆	◆	■	◆	■	■
	Dabigatran	◆	■	■	■	■	■	■
	Ticagrelor	◆	■	■	●	■	◆	■
	Warfarin	◆	◆	◆	◆	◆	◆	◆
Beta blockers	Atenolol	◆	◆	◆	◆	◆	◆	◆
	Bisoprolol	◆	◆	◆	■	◆	◆	■
	Carvedilol	■	■	■	■	◆	■	■
	Propranolol	◆	◆	◆	◆	◆	◆	◆

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Drug-Drug interactions: HCV DAAs and cardiovascular drugs

		SOF	LDV/ SOF	SOF/ VEL	OBV/PT V/RTV+ DSV	GZR/ EBR	DCV	SMV
Calcium channel blockers	Amlodipine	◆	■	■	■	■	■	■
	Diltiazem	◆	■	■	■	◆	■	■
	Nifedipine	◆	◆	◆	■	◆	■	■
Hypertension and heart failure agents	Aliskiren	◆	■	■	●	◆	■	■
	Candesartan	◆	◆	◆	■	■	◆	◆
	Doxazosin	◆	◆	◆	■	◆	◆	■
	Enalapril	◆	◆	◆	■	◆	◆	◆

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Drug-Drug interactions: HCV DAAs and central nervous system

	SOF	LDV/ SOF	SOF/ VEL	OBV/PT V/RTV+ DSV	GZR/ EBR	DCV	SMV
Anti-depressants	Amitriptyline	◆	◆	■	◆	◆	◆
	Citalopram	◆	◆	◆	◆	◆	◆
	Duloxetine	◆	◆	◆	◆	◆	◆
	Escitalopram	◆	◆	◆	◆	◆	◆
	Fluoxetine	◆	◆	◆	◆	◆	◆
	Paroxetine	◆	◆	◆	◆	◆	◆
	Setraline	◆	◆	◆	■	◆	◆
	Trazodone	◆	◆	◆	■	◆	■
	Trimipramine	◆	◆	◆	◆	◆	◆
	Venlafaxine	◆	◆	◆	■	◆	◆

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Drug-Drug interactions: HCV DAAs and central nervous system

	SOF	LDV/ SOF	SOF/ VEL	OBV/PT V/RTV+ DSV	GZR/ EBR	DCV	SMV
Anti-psychotics	Amisulpiride	◆	◆	◆	■	◆	◆
	Aripiprazole	◆	◆	◆	■	◆	■
	Chlorpromazine	◆	◆	◆	■	◆	◆
	Clozapine	◆	◆	◆	■	◆	■
	Flupentixol	◆	◆	◆	■	◆	◆
	Haloperidol	◆	◆	◆	■	◆	■
	Olanzapine	◆	◆	◆	■	◆	◆
	Paliperidone	◆	■	◆	■	■	■
	Quetiapine	◆	◆	◆	●	■	■
	Risperidone	◆	◆	◆	■	◆	■
	Zuclopentixol	◆	◆	◆	■	◆	◆

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Drug-Drug interactions: HCV DAAs immunosuppressants

	SOF	LDV/ SOF	SOF/ VEL	OBV/PT V/RTV+ DSV	GZR/ EBR	DCV	SMV
Azathioprine	◆	◆	◆	◆	◆	◆	◆
Cyclosporine	◆	◆	◆	■	●	◆	●
Etanercept	◆	◆	◆	◆	■	◆	◆
Everolimus	◆	■	■	●	■	■	■
Mycophenolate	◆	◆	◆	■	◆	◆	◆
Sirolimus	◆	◆	◆	■	■	◆	■
Tacrolimus	◆	◆	◆	■	■	◆	■

SOF: sofosbuvir; LDV: ledipasvir; VEL: velpatasvir; OBV: ombitasvir; PTV: paritepravir; DSV: dasabuvir; GZR: grazoprevir; EBR: elbasvir; DCV: daclatasvir; SMV: simeprevir




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Drug-Drug interactions: HIV ARVs

		SOF	LDV/ SOF	SOF/ VEL	OBV/PT V/RTV+ DSV	GZR/ EBR	DCV	SMV
NRTIs	Abacavir	◆	◆	◆	◆	◆	◆	◆
	Emtricitabine	◆	◆	◆	◆	◆	◆	◆
	Lamivudine	◆	◆	◆	◆	◆	◆	◆
	Tenofovir	◆	■	■	◆	◆	◆	◆
NNRTIs	Efavirenz	◆	■	●	●	●	■	●
	Etravirine	◆	◆	●	●	●	■	●
	Nevirapine	◆	◆	●	●	●	■	●
	Rilpivirine	◆	◆	◆	■	◆	◆	◆

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Drug-Drug interactions: HIV ARVs

		SOF	LDV/ SOF	SOF/ VEL	OBV/PT V/RTV+ DSV	GZR/ EBR	DCV	SMV
Protease inhibitors	Atazanavir; atazanavir/r; atazanavir/cobicistat	◆	◆	◆	■	●	■	●
	Darunavir/r darunavir/cobicistat	◆	◆	◆	■	●	◆	●
	Lopinavir/r	◆	◆	◆	●	●	◆	●
Entry/integrase inhibitors	Dolutegravir	◆	◆	◆	◆	◆	◆	◆
	Elvitegravir/cobi/emtricitabine/TDF	◆	■	■	●	●	■	●
	Elvitegravir/cobi/emtricitabine/TAF	◆	◆	◆	●	●	■	●
	Maraviroc	◆	◆	◆	■	◆	◆	◆
	Raltegravir	◆	◆	◆	◆	◆	◆	◆

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-  No clinically significant interaction expected
-  Potential interaction which may require a dosage adjustment, altered timing of administration or additional monitoring
-  These drugs should not be co-administered.



Drug-Drug interactions: HCV DAAs and illicit recreational drugs

	SOF	LDV/ SOF	SOF/ VEL	OBV/PT V/RTV+ DSV	GZR/ EBR	DCV	SMV
Amphetamine	◆	◆	◆	■	◆	◆	◆
Cannabis	◆	◆	◆	■	◆	◆	■
Cocaine	◆	◆	◆	■	◆	◆	■
Diamorphine	◆	◆	◆	■	◆	◆	◆
Diazepam	◆	◆	◆	■	◆	◆	■
Gamma-hydroxybutyrate	◆	◆	◆	■	◆	◆	■
Ketamine	◆	◆	◆	■	◆	◆	■
MDMA (ecstasy)	◆	◆	◆	■	◆	◆	◆
Methamphetamine	◆	◆	◆	■	◆	◆	◆
Phencyclidine (PCP)	◆	◆	◆	■	◆	◆	■
Temazepam	◆	◆	◆	◆	◆	◆	◆

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IFN-free combination treatment regimens available as valuable options for each HCV genotype

Combination regimen	SOF + RBV	LDV/SOF ± RBV	SOF/VEL ± RBV	OBV/PTV/RTV+ DSV ± RBV	OBV/PTV/RTV ± RBV	GZR/EBR	SOF + DCV ± RBV	SOF + SMV ± RBV
GT1	✗	✓	✓	✓	✗	✓	✓	Suboptimal
GT2	Suboptimal	✗	✓	✗	✗	✗	✓	✗
GT3	Suboptimal	✗	✓	✗	✗	✗	✓	✗
GT4	✗	✓	✓	✗	✓	✓	✓	✗
GT5	✗	✓	✓	✗	✗	✗	✓	✓
GT6	✗	✓	✓	✗	✗	✗	✓	✗



Treatment initiation and monitoring

- Anti-HCV antibodies are the first line diagnostic test for HCV infection.
- HCV core antigen** is a surrogate marker of HCV replication and can be used instead of HCV RNA to diagnose acute or chronic infection when HCV RNA assays are not available or not affordable (core antigen assays are slightly less sensitive than HCV RNA assays for detection of viral replication).
- In patients treated with an IFN-free regimen, HCV RNA or HCV core antigen levels monitoring can be simplified:

Baseline	Week 2	Week 4	EOT	SVR
✓	optional	optional	✓	✓



Treatment recommendation

GT1

GT2/3

GT4

GT5/6

Patients with decompensated cirrhosis, MELD Guidance

Patients with post-liver transplant recurrence

Patients with post-liver transplant recurrence

Patients with renal impairment

Patients with non-hepatic solid organ transplant recipients

Patients who failed to achieve SVR on prior antiviral therapy

Patients with acute hepatitis C

Treatment recommendations for HBV/HCV co-infection

Patients who are active drug addicts and/or on stable maintenance substitution

 Click on BOXES to go to section



Treatment recommendation for GT1 patients without and with compensated cirrhosis

Treatment recommendations for GT1 patients without cirrhosis						
GT	TN/TE	LDV/SOF	SOF/VEL	OBV/PTV/ RTV+ DSV	GZR/EBR	SOF + DCV
GT1a	TN	8-12 weeks	12 weeks	12 weeks + RBV	12 weeks, if HCV RNA ≤800,000 (5.9 log) IU/ml or 16 weeks + RBV if HCV RNA >800,000 (5.9 log) IU/ml ^b	12 weeks
	TE	12 weeks + RBV ^a 24 weeks				12 weeks + RBV 24 weeks
GT1b	TN	8-12 weeks	12 weeks	8-12 weeks	12 weeks	12 weeks
	TE	12 weeks		12 weeks		

Treatment recommendations for GT1 patients with compensated cirrhosis						
GT	TN/TE	LDV/SOF	SOF/VEL	OBV/PTV/ RTV+ DSV	GZR/EBR	SOF + DCV
GT1a	TN	12 weeks	12 weeks	24 weeks + RBV	12 weeks, if HCV RNA ≤800,000 (5.9 log) IU/ml or 16 weeks + RBV if HCV RNA >800,000 (5.9 log) IU/ml ^b	12 weeks
	TE	12 weeks + RBV ^a 24 weeks				12 weeks + RBV 24 weeks
GT1b	TN TE	12 weeks	12 weeks	12 weeks	12 weeks	12 weeks

a. Add ribavirin only in patients with RASs that confer high-level resistance to NS5A inhibitors at baseline if RAS testing available.

b. Prolong to 16 weeks and add ribavirin only in patients with RASs that confer resistance to elbasvir at baseline if RAS testing available.

- For GT1a and GT1b non cirrhotic patients, LDV/SOF should be used for 12 weeks without RBV. LDV/SOF + RBV for 12 weeks or LDV/SOF (without ribavirin) for 24 weeks should be considered for previously treated patients with uncertain subsequent retreatment options
- 8 weeks OBV/PTV/RTV+ DSV is not an EMA recommended regimen for GT1b



Treatment recommendation for GT2 and GT3 patients without and with compensated cirrhosis

Treatment recommendations for GT2 and GT3 patients without cirrhosis			
GT	TN/TE	SOF/VEL	SOF + DCV
GT2	TN/TE	12 weeks	12 weeks
GT3	TN	12 week	12 weeks
	TE	12 week + RBV ^a 24 week	12 week + RBV ^a 24 week

Treatment recommendations for GT2 and GT3 patients with compensated cirrhosis			
GT	TN/TE	SOF/VEL	SOF + DCV
GT2	TN/TE	12 weeks	12 weeks
GT3	TN	12 week	24 weeks + RBV
	TE	12 week + RBV ^a 24 week	

a. Add ribavirin only in patients with NS5A RAS Y93H at baseline if RAS testing available.



Treatment recommendation for GT4, GT5 or GT6 patients without and with compensated cirrhosis

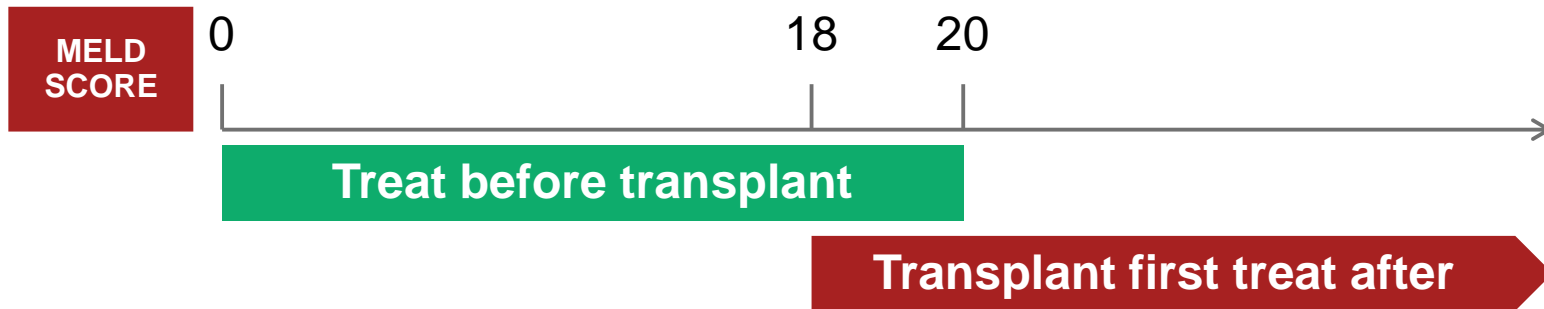
Treatment recommendations for GT4 patients without and with compensated cirrhosis							
GT	TN/TE	LDV/SOF	SOF/VEL	OBV/PTV/ RTV	GZR/EBR	SOF + DCV	SOF + SMV
GT4	TN	12 weeks	12 weeks	12 weeks + RBV	12 weeks	12 weeks	12 weeks
	TE	12 weeks + RBV 24 weeks			12 weeks, if HCV RNA ≤ 800,000 (5.9log) IU/ml or 16 weeks + RBV if HCV RNA > 800,000 (5.9log) IU/ml	12 weeks + RBV 24 weeks	12 weeks + RBV 24 weeks

Treatment recommendations for GT5 or GT6 patients without and with compensated cirrhosis				
GT	TN/TE	LDV/SOF	SOF/VEL	SOF + DCV
GT5 or GT6	TN	12 weeks	12 weeks	12 weeks
	TE	12 weeks + RBV 24 weeks		12 weeks + RBV 24 weeks



Treatment recommendation for Patients with decompensated cirrhosis, no HCC, with an indication for liver transplantation

MELD Score Guidance



- Patients with decompensated cirrhosis without HCC awaiting liver transplantation with a MELD score $\geq 18-20$ can be treated before transplantation if the waiting time on the transplant list exceeds 6 months, depending on the local situation.
- Patients with decompensated cirrhosis without HCC awaiting liver transplantation with a MELD score $\geq 18-20$ should be transplanted first, without antiviral treatment. HCV infection should be treated after liver transplantation.



Treatment recommendation for Patients with decompensated cirrhosis, no HCC, with an indication for liver transplantation

Patients with decompensated cirrhosis, no HCC, with an indication for liver transplantation MELD score <18-20 treat before liver transplantation			
GT	LDV/SOF + RBV	SOF/VEL + RBV	SOF + DCV + RBV
GT1	12 weeks	12 weeks	12 weeks
GT2	-	12 weeks	12 weeks
GT3	-	24 weeks	24 weeks
GT4	12 weeks	12 weeks	12 weeks
GT5	12 weeks	12 weeks	12 weeks
GT6	12 weeks	12 weeks	12 weeks

Daily ribavirin recommended weight-based dose is 1000 or 1200 mg in patients <75 kg or ≥75 kg, respectively. Ribavirin can be started at the dose of 600 mg daily and the dose subsequently adjusted depending on tolerance.

Patients with decompensated cirrhosis with contraindications to the use of RBV or with poor tolerance to ribavirin on treatment should receive the fixed-dose combination of LDV/SOF (GT1, 4, 5 or 6), the fixed-dose combination of SOF/VEL (all genotypes), or the combination of SOF + DCV (all genotypes) for 24 weeks without RBV.



Treatment recommendation for Patients with post-liver transplant recurrence

Patients with post-liver transplant recurrence without cirrhosis (F0-F3), with compensated (CTP A) and decompensated (CTP B and CTP C) cirrhosis			
GT	LDV/SOF + RBV	SOF/VEL + RBV	SOF + DCV + RBV
GT1	12 weeks	12 weeks	12 weeks
GT2	-	12 weeks	12 weeks
GT3	-	24 weeks	24 weeks
GT4	12 weeks	12 weeks	12 weeks
GT5	12 weeks	12 weeks	12 weeks
GT6	12 weeks	12 weeks	12 weeks

- Patients with decompensated cirrhosis with contraindications to the use of RBV or with poor tolerance to ribavirin on treatment should receive the fixed-dose combination of LDV/SOF (GT1, 4, 5 or 6), the fixed-dose combination of SOF/VEL (all genotypes), or the combination of SOF + DCV (all genotypes) for 24 weeks without RBV.



Treatment recommendation for Patients with renal impairment

Patients with severe renal impairment (eGFR <30ml/min/1.73m ²) or ESRD on haemodialysis without an indication for kidney transplantation					
GT	OBV/PTV/ RTV+ DSV	GZR/EBR	OBV/PTV/ RTV	SOF/VEL	SOF + DCV
GT1a	12 weeks + RBV	12 weeks + RBV	-	-	-
GT1b	12 weeks	12 weeks	-	-	-
GT2	-	-	-	12 weeks	12 weeks
GT3	-	-	-	12 weeks + RBV ^a 24 weeks ^a	12 weeks + RBV ^a 24 weeks ^a
GT4	-	12 weeks	12 weeks	-	-

a. Only if treatment is urgently needed in patients with severe renal impairment (eGFR <30 ml/min/1.73 m²) or with end-stage renal disease on haemodialysis without an indication for kidney transplantation infected

- Patients with mild to moderate renal impairment (eGFR ≥30 ml/min/1.73 m²) with HCV infection should be treated according to the general recommendations. No dose adjustments of HCV DAAs are needed, but these patients should be carefully monitored.
- SOF_r should be used with caution in patients with an eGFR <30 ml/min/1.73 m² or with end-stage renal disease because no dose recommendation can currently be given for these patients



Treatment recommendation for non-hepatic solid organ transplant recipients

Patients with non-hepatic solid organ transplant recipients			
GT	LDV/SOF	SOF/VEL	SOF + DCV
GT1	✓	✓	✓
GT2	✗	✓	✓
GT3	✗	✓	✓
GT4	✓	✓	✓
GT5	✓	✓	✓
GT6	✓	✓	✓

No need for immunosuppressant drug dose adjustments (with the probable exception of everolimus)



Treatment recommendations for retreatment of HCV who failed to achieve SVR on prior antiviral therapy containing one or several DAAs

Patients who failed to achieve SVR with a PegIFN- α and telaprevir, or boceprevir, or simeprevir							
	LDV/SOF	SOF/VEL	OBV/PTV/ RTV + DSV	OBV/PTV/ RTV	GZR/EBR	SOF + DCV	SOF + SMV
GT1	12 weeks + RBV	12 weeks + RBV	-	-	-	12 weeks + RBV	-

Patients who failed to achieve SVR with a SOF + SMV							
	LDV/SOF	SOF/VEL	OBV/PTV/ RTV + DSV	OBV/PTV/ RTV	GZR/EBR	SOF + DCV	SOF + SMV
GT1 or GT4	12 weeks + RBV (F0-F2) or 24 weeks + RBV (F3-F4)	12 weeks + RBV (F0-F2) or 24 weeks + RBV (F3-F4)	-	-	-	12 weeks + RBV (F0-F2) or 24 weeks + RBV (F3-F4)	-



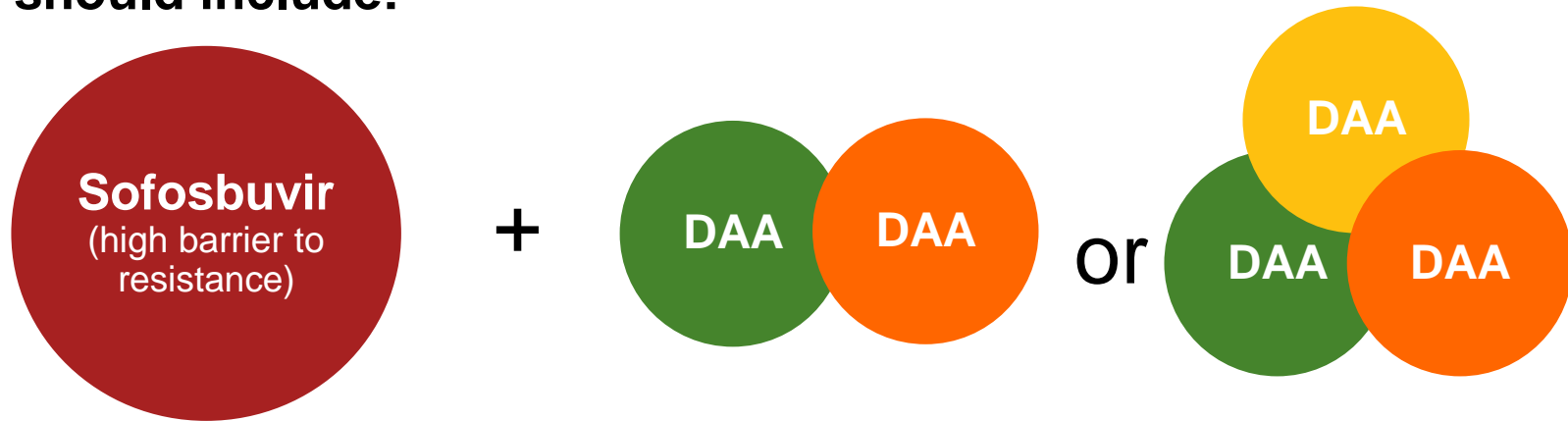
Treatment recommendations for retreatment of HCV who failed to achieve SVR on prior antiviral therapy containing one or several DAAs

Patients who failed to achieve SVR with SOF + RBV or SOF + RBV + PegIFN- α						
	LDV/SOF	SOF/VEL	OBV/PTV/ RTV \pm DSV	GZR/EBR	SOF + DCV	SOF + SMV
GT1 or GT4	12 weeks + RBV (F0-F2) or 24 weeks + RBV (F3-F4)	12 weeks + RBV (F0-F2) or 24 weeks + RBV (F3-F4)	12 weeks + RBV (F0-F2) or 24 weeks + RBV (F3-F4) (For GT4 no DSV)	12 weeks +RBV (F0-F2 with HCV RNA \leq 800,000 (5.9 log) IU/ml) or 24 weeks +RBV (F0-F2 with HCV RNA>800,000 (5.9 log) IU/ml and F3-F4)	12 weeks + RBV (F0-F2) or 24 weeks + RBV (F3-F4)	-12 weeks + RBV (F0-F2) or 24 weeks + RBV (F3-F4)
GT2 or GT3	-	12 weeks + RBV (F0-F2) or 24 weeks + RBV (F3-F4)	-	-	12 weeks + RBV (F0-F2) or 24 weeks + RBV (F3-F4)	-
GT5 or GT6	12 weeks + RBV (F0-F2) or 24 weeks + RBV (F3-F4)	12 weeks + RBV (F0-F2) or 24 weeks + RBV (F3-F4)	-	-	12 weeks + RBV (F0-F2) or 24 weeks + RBV (F3-F4)	-



Treatment recommendations for retreatment of HCV who failed to achieve SVR on prior antiviral therapy containing one or several DAAs (LDV, VEL, OMV, EBR, DCV)

- Patients who failed to achieve SVR with a NS5A-based regimen should include:



Treatment
Duration

12 weeks + RBV

24 weeks + RBV in more difficult-to-cure patients (F3 fibrosis or cirrhosis)

24 weeks (no RBV) in those who have a contraindication to or do not tolerate RBV

Treatment recommendations for retreatment of HCV who failed to achieve SVR on prior antiviral therapy containing one or several DAAs

Patients who failed to achieve SVR with a NS5A-based regimen (LDV, VEL, OMV, EBR, DCV)

	SOF/VEL + RBV	SOF + OMV/PTV/RTV + DSV	SOF + OMV/PTV/RTV +RBV	SOF + GRZ/EBV + RBV	SOF + DCV + SMV + RBV
GT1a		24 weeks	-	24 weeks	24 weeks
GT1b		F0–F2 12 weeks F3–F4 24 weeks	-	F0–F2 12 weeks F3–F4 24 weeks	
GT 3	24 weeks	-	-	-	-
GT 4				F0–F2 12 weeks F3–F4 24 weeks	
GT 5/6	24 weeks	-	-	-	-



Treatment recommendations for acute hepatitis C

	Patients with acute monoinfection hepatitis C		
	LDV/SOF	SOF/VEL	SOF + DCV
GT1, 4, 5 and 6	8 weeks	8 weeks	8 weeks
All genotypes	-	8 weeks	8 weeks

	Patients with acute hepatitis C and HIV coinfection and/or baseline HCV RNA level > 1 million IU/ml (6.0 log IU/ml)		
	LDV/SOF	SOF/VEL	SOF + DCV
GT1, 4, 5 and 6	12 weeks	12 weeks	12 weeks
All genotypes	-	12 weeks	12 weeks



Treatment recommendations for HBV/HCV coinfection

- Patients commencing DAA-based treatment for HCV should be tested for HBs antigen, anti-HBc antibodies and anti-HBs antibodies.
- If HBs antigen is present or if HBV DNA is detectable in HBs antigen-negative, anti-HBc antibody-positive patients (“occult” hepatitis B), concurrent HBV nucleoside/nucleotide analogue therapy is indicated.
- Assiduous monitoring of serum aminotransferase levels is indicated in anti-HBs and anti-HBc antibody-positive patients.
- Patients with HBV coinfection should be treated with the same regimens, following the same rules as HCV monoinfected patients



Treatment recommendations of active drug addicts and patients on stable maintenance substitution

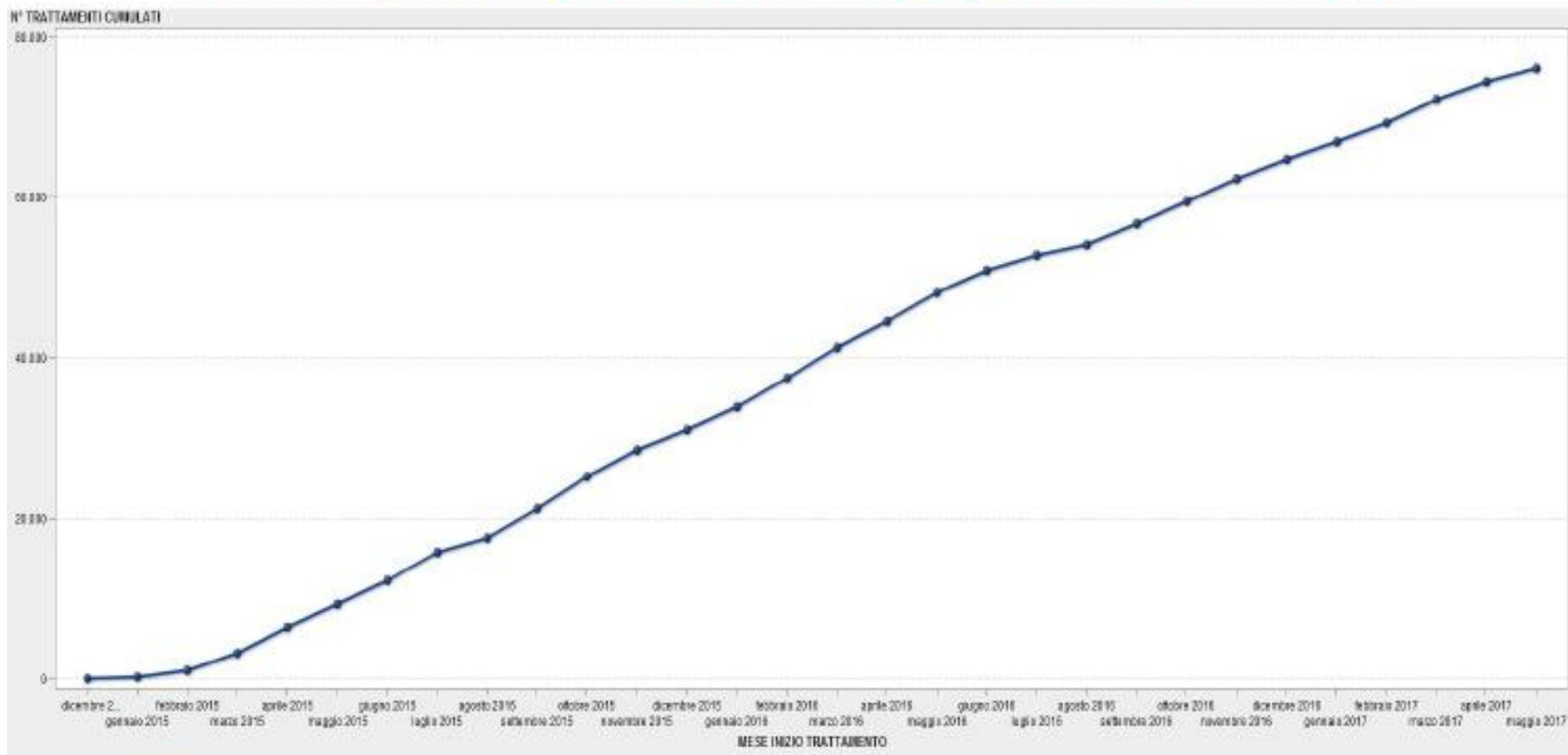
- PWIDs should be routinely and voluntarily tested for anti-HCV antibodies and if negative, annually.
- PWIDs should be provided with clean drug injecting equipment and access to opioid substitution therapy as part of widespread comprehensive harm reduction programs, including in prisons.
- HCV treatment for PWIDs should be considered on an individualized basis and delivered within a multidisciplinary team setting.
- **The anti-HCV regimens that can be used in PWIDs are the same as in non-PWIDs.** They do not require specific methadone and buprenorphine dose adjustment, but monitoring for signs of opioid toxicity or withdrawal should be undertaken.





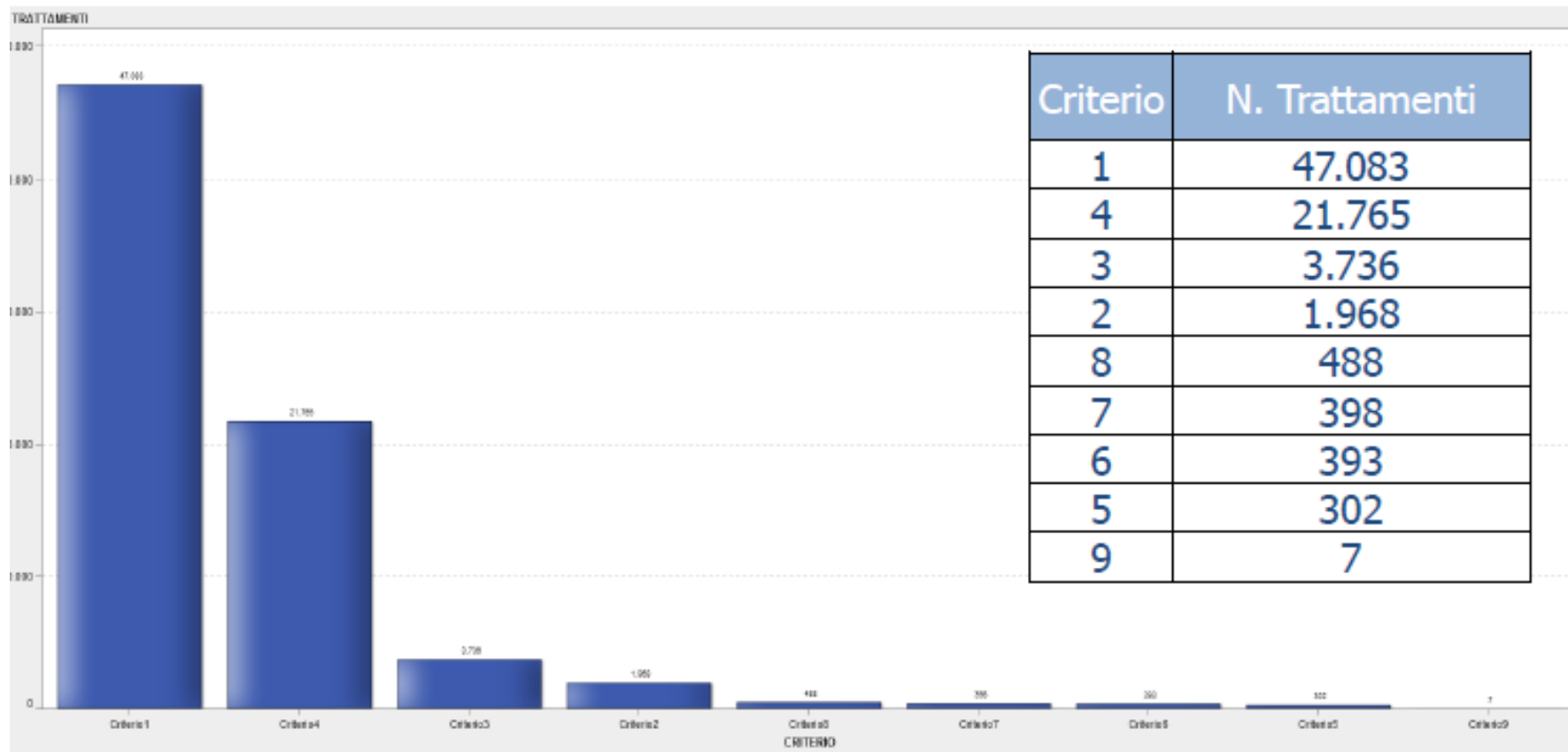
1. Pazienti con cirrosi in classe di Child A o B e/o con HCC con risposta completa a terapie resettive chirurgiche o loco-regionali non candidabili a trapianto epatico e nei quali la malattia epatica sia determinante per la prognosi;
2. Pazienti con recidiva di epatite dopo trapianto di fegato con fibrosi METAVIR ≥ 2 (o corrispondente Ishak) o fibrosante colestatica;
3. Pazienti con epatite cronica con gravi manifestazioni extra-epatiche HCV-correlate (sindrome crioglobulinemica con danno d'organo, sindromi linfoproliferative a cellule B);
4. Pazienti con epatite cronica con fibrosi METAVIR F3 (o corrispondente Ishak);
5. Pazienti in lista per trapianto di fegato con cirrosi MELD < 25 e/o con HCC all'interno dei criteri di Milano con la possibilità di un'attesa in lista di almeno 2 mesi;
6. Pazienti con epatite cronica dopo trapianto di organo solido (non fegato) o di midollo con fibrosi METAVIR ≥ 2 (o corrispondente Ishak).
7. Pazienti con epatite cronica con fibrosi METAVIR F0-F2 (o corrispondente Ishak)

Trend cumulativo dei trattamenti avviati



76.140 «avviati» sono i trattamenti (solo pazienti eleggibili) con almeno una scheda di Dispensazione farmaco

Trattamenti avviati per criterio



NB: I trattamenti avviati con il precedente criterio 7 sono stati distribuiti, sulla base della stadiazione METAVIR, nei nuovi criteri 7 e 8

NUOVI CRITERI AIFA MARZO 2017

- Criterio 1:** Pazienti con cirrosi in classe di Child A o B e/o con HCC con risposta completa a terapie resettive chirurgiche o loco-regionali non candidabili a trapianto epatico nei quali la malattia epatica sia determinante per la prognosi.
- Criterio 2:** Epatite ricorrente HCV-RNA positiva del fegato trapiantato in paziente stabile clinicamente e con livelli ottimali di immunosoppressione.
- Criterio 3:** Epatite cronica con gravi manifestazioni extra-epatiche HCV-correlate (sindrome crioglobulinemica con danno d'organo, sindromi linfoproliferative a cellule B, insufficienza renale).
- Criterio 4:** Epatite cronica con fibrosi METAVIR F3 (o corrispondente Ishak).
- Criterio 5:** In lista per trapianto di fegato con cirrosi MELD <25 e/o con HCC all'interno dei criteri di Milano con la possibilità di una attesa in lista di almeno 2 mesi.
- Criterio 6:** Epatite cronica dopo trapianto di organo solido (non fegato) o di midollo in paziente stabile clinicamente e con livelli ottimali di immunosoppressione.
- Criterio 7:** Epatite cronica con fibrosi **METAVIR F2**.
- Criterio 8:** Epatite cronica con fibrosi **METAVIR F0-F1** (o corrispondente Ishak) e/o comorbilità a rischio di progressione del danno epatico [coinfezione HBV, coinfezione HIV, malattie croniche di fegato non virali, diabete mellito in trattamento farmacologico, obesità (body mass index ≥ 30 kg/m²), emoglobinopatie e coagulopatie congenite].
- Criterio 9:** Operatori sanitari infetti.
- Criterio 10:** Epatite cronica o cirrosi epatica in paziente con insufficienza renale cronica in trattamento emodialitico.
- Criterio 11:** Epatite cronica nel paziente in lista d'attesa per trapianto di organo solido (non fegato) o di midollo

Decisioni cliniche e organizzative 2/5/17

*DOCUMENTO DI INDIRIZZO
per la definizione delle strategie terapeutiche
da applicare sul breve termine per:*

**Antivirali diretti
nella terapia dell'epatite C cronica**

- Il GdL, in seguito al recente allargamento dei criteri di rimborsabilità, alla disponibilità di nuovi trattamenti e ai nuovi accordi negoziali per i farmaci disponibili, sulla base delle caratteristiche e della numerosità della casistica da trattare ha stabilito di:
definire criteri omogenei di arruolamento dei pazienti, con l'obiettivo di:
- - garantire, sia per i pazienti già in carico ai singoli Centri che per i pazienti incidenti, l'accesso alla terapia nel più breve tempo possibile a tutti coloro che ne hanno maggiore necessità clinica;
- - programmare, in occasione del controllo ambulatoriale periodico, per tutti i pazienti afferenti al singolo Centro la tempistica del trattamento.
- A tal fine, applicando i principi di priorità clinica sopra descritti, e a partire dai criteri di eleggibilità dei registri AIFA dei DAA, si è deciso di trattare i pazienti che presentano le seguenti caratteristiche: Criteri 1-2-3-4-5-6-7-8(con co-patologie)-9-10-11
- Una volta esauriti i criteri sopra elencati, si inizierà a trattare i pazienti con Fibrosi META-VIR F0-F1 che non presentano comorbilità

CRITERIO 8 MODIFICATO RER

- **Criterio 8:** epatite cronica con fibrosi META-VIR F0-F1 (o corrispondente Ishak) e comorbidità a rischio di progressione del danno epatico [coinfezione HBV, coinfezione HIV, malattie croniche di fegato non virali, diabete mellito in trattamento farmacologico, obesità (BMI ≥ 30 kg/m²), emoglobinopatie e coagulopatie congenite], o in pazienti oncologici che necessitano di chemioterapia o in donne in età fertile.